REMARKS/ARGUMENTS

The non-final Office Action mailed December 13, 2007 has been carefully reviewed and these remarks are responsive to that office action. Claims 1-26 are currently pending. Claims 7-9 and 12-20 were withdrawn from further consideration as being drawn to a nonelected species, and Applicant timely traversed the restriction (election) requirement in the reply filed May 30, 2006. Claims 1-6, 10, 11 and 21-25 were examined in the non-final Office Action mailed December 13, 2007. Claims 1 and 2 have been amended to correct informalities in accordance with the request in the Office Action. Claims 21-25 have been amended to clarify specific receptor sites. New dependent claim 26 has been added, and depends from independent claim 1.

Claim Objections

Claims 1 and 2 were objected to because of the following informalities of having parenthesis in the term "(% w/v)" in claim 1 and claim 2. The parenthesis in claims 1 and 2 in the term "(% w/v)" has been removed in accordance with the Examiner's request.

Claims 21-25 were objected to because they were deemed to be redundant and appeared to recite the same limitation as claim 1. It is respectfully submitted that claims 21-25 are not redundant and that they do not recite the same limitation as claim 1. Claim 1 recites a Markush group as an "anticonvulsant pharmaceutical composition for nasal administration having a binding affinity for at least one receptor site selected from the group consisting of sting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate- alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate-*N*-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate- *N*-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2) . . ." Claims 21-25 each depend from claim 1, and each specifies that the composition has binding affinity for a particular receptor site from the Markush group of claim 1. Thus, each of claims 21-25 further limit claim 1, and are thus not redundant. (See MPEP 2173.05(h)) It is respectfully submitted that the objection to claims 21-25 be withdrawn. New claim 26 similarly depends from claim 1, and is not redundant.

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Claim Rejections – 35 USC 112 (1st and 2nd paragraphs)

Claims 1-6, 10, 11 and 21-25 were rejected under 35 U.S.C. 112, first paragraph, because it was deemed that the specification, while being enabling for a pharmaceutical composition for the prophylactic treatment of migraines comprising an aqueous extract of *Sapindus trifoliatus* pericap (0.1-1% w/v) and *Emblica officinalis* (0.1-1 % w/v), does not reasonably provide enablement for an anticonvulsant pharmaceutical composition for nasal administration having a binding affinity for at least one receptor site selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate side, Glutamate: N-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate-N-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2), consisting essentially of: i. an aqueous, alcoholic, or hydroalcoholic extract of the pericarp of the fruit of *Sapindus trifoliatus*, comprising from 0.001 to 1.0 % w/v of hederagenin, and ii. at least one pharmaceutically acceptable additive, nor does it reasonably provide enablement for an anticonvulsant pharmaceutical composition, for nasal administration according to claim 1, being suitable for prophylactic treatment of migraine mediated through its anticonvulsant activity. The Office Action states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification as originally filed does, however, enable more to one of ordinary skill in the art more than the Office Action gives credit for. The specification as originally filed certainly enables the claimed invention to one of ordinary skill in the art. As specified by claim 1, the claimed composition possesses affinity for at least one receptor selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate-*N*-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate-*N*-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2).

As explained in the Declaration of Sudershan K. Arora, submitted herewith, the specification as originally filed enables one of ordinary skill in the art to practice the claimed

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invention. The proper application of the *Wands* factors in the present case demonstrates such enablement, as further discussed below.

Nature of the Invention: While the nature of the invention may be deemed complex, commensurate with the nature of the invention is the level of ordinary skill in the art. One of ordinary skill in the art, having the benefit of the application as originally filed as well as the Chikara reference, would certainly be able to practice the claimed invention without undue experimentation. Indeed, all one of ordinary skill in the art need do is substitute the claimed invention for what is taught in Chikara.

Table 1 of the specification as originally filed shows the benefit of the claimed invention. The specification further details how a composition comprising an aqueous, alcoholic, or hydroalcoholic extract of the pericarp of the fruit of *Sapindus trifoliatus*, comprising of total saponins expressed as hederagenin from 0.001 to 1.0 % w/v , and ii. at least one pharmaceutically acceptable additive, is capable of prophylactic treatment of migraines. *See* page 11, lines 16-20 and page 17, lines 25-29 of the application as originally filed. There is no requirement for patentability to demonstrate a mechanism of action, only that the specification enables one of ordinary skill in the art to practice the claimed invention without undue experimentation. Furthermore, although the animal test examples did not include alcoholic and hydroalcoholic extracts of the fruit of *Sapindus trifoliatus*, it was not necessary for them to do so because all three types of extracts contained the same active ingredients. *See* Declaration of Arora and page 16, line 6 through page 17, line 13 of the specification as originally filed.

Breadth of the Claims: The claims are no broader than the enabling specification. *See* Declaration of Arora. The Office Action does not discuss this factor in connection with the present application. Instead, the Office Action appears to discuss this factor in connection with wholly unrelated application, i.e., one that claims a "transfer factor" wherein the "transfer factor is a mammalian transfer factor, and the at least one support component is bitter melon and Indian kino . . . "

Guidance of the Specification and Existence of Working Examples: The Office Action recognizes that the specification describes an aqueous extract of *Sapindus trifoliatus* that displays

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binding affinity for $GABA_A$ agonistic site in bovine cerebellum, and in Glutamate AMPA site in rat forebrain, Glutamate Kainate site in rat forebrain, Glutamate NMDA site in rat forebrain, Glutamate NMDA Glycine (strychenine-insensitive site) in rat cortex and hippocampus, GABA chloride TBOB in rat cortex, Glutamate chloride in rat cerebellum, and Sodium site 2 in rat forebrain when in higher concentrations (see page 19, Table 1). The Office Action states that there is no description of how these studies were conducted or how the results were obtained. As explained in the Declaration of Arora, one of ordinary skill in the art, having the benefit of the specification as originally filed, would know how to conduct such studies and obtain results from such studies.

(1) Working examples of extracts for migraine prophylaxis: The Examiner has commented that the specification lacks working examples with aqueous, alcoholic and hydroalcoholic extracts of pericarp of Sapindus trifoliatus with regard to its prophylactic use in migraine. Also there is no example of alcoholic and hydroalcoholic extracts with respect to prophylactic use in migraine. It is respectfully submitted that pages 14 to 27 of the specification as originally filed describes the composition as well as the extract and working examples. The preparation of the aqueous extract as well as the alcoholic and aqueous alcoholic extract is provided in examples 1 to 4. Example 6 provides a preparation of nasal spray i.e. the composition for nasal route. At page 18 the *in vitro* binding affinity of the extract of Sapindus trifoliatus (3) (which as described at page 14 is dry powder obtained on lyophilization of aqueous extract of Sapindus trifoliatus) is described. It is mentioned that the said activity is conducted at Novascreen®, USA, for GABA Agonist Site, Glutamate AMPA Site, Glutamate Kainate Site, Glutamate NMDA Agonist site, Glutamate NMDA Glycine (Strychnine Insensitive) Site and Sodium Channel. The basis of determining the binding affinity as done by Novascreen®, USA, has been provided. In the same page the use of alcohol extract and hydro alcoholic is also mentioned. The results are provided in Table 1 at page 19. This result shows the activity of the aqueous extract on the various sites. It is further mentioned at page 19 as to how dose dependent binding affinity for various receptor sites takes place. The *in vivo* studies with the same extract indicates prevention of seizure spread on intranasal administration. The anticonvulsant activity

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for the extract by administering the same intra nasally is demonstrated on male Wistar Rat at page 20 and 21 of the specification as originally filed. This shows the test compounds' ability to inhibit MES induced seizure spread. This demonstrates the anticonvulsive activity of the extract (3). Further disclosure at pages 22 and 23 of the specification as originally filed shows that the anticonvulsive activity of extract (3) demonstrated in MES model by intranasal route is without sedation and does not induce or potentiate convulsion of chemical or electrical origin. That anticonvulsive agents act for prophylactic treatment of migraine is described in the Background of the Invention at pages 5, 6 and 7 of the specification as originally filed. Accordingly, it is evident that the present extract of *Sapindus trifoliatus* would act as prophylactic treatment for migraine. Pages 26 and 27 of the specification as originally filed describes that unit formula for nasal spray containing extract of *Sapindus trifoliatus* (3) is prepared and used against migraine. That the active namely the extract (3) acts by binding the specific site is demonstrated and the composition comprises the same active is also disclosed. Accordingly a person skilled in the art would easily prepare composition comprising the said active which would act by binding to specific receptor sites and bring about anticonvulsive activity which would be required for prophylactic treatment of migraine. In the present case, since the anticonvulsive activity is already known to have effect on migraine, the applicants have provided description of particular composition with extract of *Sapindus trifoliatus*, which by having specific binding affinity for defined receptor sites brings about anticonvulsant activity which is known to act as prophylactic treatment for migraine.

It is further submitted that the present extract (and hence the formulation/ composition essentially consisting of the same) is useful for the prophylaxis of migraine attack is further supported by the clinical findings, which is noted in the Declaration of Arora accompanying this Response. The mechanism of action that demonstrates the effect of this composition is explained on page 5, lines 23-28, page 6, lines 21-31, and page 20, lines 11-22 of the specification as originally filed.

Applicants respectfully disagree with the Examiner's comment of lack of mechanism being provided since the binding affinity through *in vitro* as well as *in vivo* anticonvulsant

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activity is described in the specification as originally filed. Accordingly it cannot be said that mechanism of action that demonstrate the claimed composition having the claimed effect is lacking. In this respect, it is respectfully submitted that the specification should also be considered while looking into enablement of disclosure. In this respect, MPEP 2164 provides:

> "Any part of the specification can support an enabling disclosure, even a background section that discusses, or even disparages, the subject matter disclosed therein. Callicrate v. Wadsworth Mfg., Inc., 427 F.3d 1361, 77 USPQ2d 1041 (Fed. Cir. 2005)(discussion of problems with a prior art feature does not mean that one of ordinary skill in the art would not know how to make and use this feature).< Determining enablement is a question of law based on underlying factual findings. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984)."

Further, the following is quoted from Callicrate v. Wadsworth Mfg., Inc., 427 F.3d 1361, 77 USPQ2d 1041 (Fed. Cir. 2005):

> "First, a patent specification may sufficiently enable a feature under § 112, ¶ 1, even if only the background section provides the enabling disclosure. See Micro Chem., 194 F.3d at 1259-60 (finding that, under a §112, ¶ 6 analysis, the claims encompass a weigh dump method despite the fact that the only disclosure of this method was in the background section); United States v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from disclosures in the patent coupled with information known in the art without undue experimentation.") (emphasis added). Indeed, if disclosure solely in the background section were insufficient to satisfy the enablement requirement of § 112, then the Examiner would likely have rejected claim 16 during prosecution of the '553 patent for lack of enablement because the only disclosure of a caulking gun-type mechanism being used in a castration tool embodiment in the '553 patent appears in the background section. See '553 patent, col. 2, ll. 1-22 (background section describing caulking gun-type mechanism in depth), col. 3, ll. 38-43 (summary section disclosing pre-formed loop embodiment, which may be used with prior art devices such as a caulking gun-type mechanism), col. 15, ll. 35-39 (detailed description section disclosing crimping embodiment in comparison to '704 patent's elongated crimping rod); Manual of Patent Examining Procedure, § 2164.04 at 2100-183 (8th Ed. Rev. 1, Feb. 2003) ("[T]he

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examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention."

It is evident from above that the disclosure in the specification as originally filed, including the Detailed Description as well as the Background of the Invention should be considered while considering enablement of disclosure.

(2) Working example with regard to the pharmaceutical composition provided nasally:

Applicants further note that the MPEP provides as follows.

2164.02 Working Example

Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic." A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

An applicant need not have actually reduced the invention to practice prior to filing. In Gould v. Quigg, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987), as of Gould's filing date, no person had built a light amplifier or measured a population inversion in a gas discharge. The Court held that "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting In re Chilowsky, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)).

The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In reBorkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

Thus it is clear from above that an example is not an absolute necessity if the disclosure in the text is in such a manner that a person skilled in the art will be able to practice the invention without undue experimentation. In the present case, the description clearly describes how to form the extracts and the composition. Also, the various types of extracts other than the aqueous form are also taught in the specification. Following the same, a person ordinary skilled in the art can easily prepare the formulation in accordance with the teachings of the specification as

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originally filed. The binding affinity of the composition is due to the extracts described in the specification, and the effect of such binding is already demonstrated. The other components of the composition is the additive which those skilled in the art will recognize does not play a role in the binding as claimed. Further, the examples teach preparation of the extract as well as the composition comprising the same.

As to the Examiner's contention that the alcoholic and the hydroalcoholic extract are not at all provided by way of working examples, applicants submit that as mentioned it is not necessary to provide working examples for each and every mode of making and using the invention. As noted in *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998), "[t]he enablement requirement is met if the description enables any mode of making and using the invention."

The enablement requirement is met in the present case since the specific extract is described. Applicants' originally filed disclosure of a working of aqueous extract, and the description of other extracts and their preparation clearly meet the enablement requirement as required by Section 112. It is further noted that the enablement requirement is often more indulgent than the written description requirement. The enablement requirement is satisfied if, given what one of ordinary skill in the art already knows, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." It would be expected that the person ordinary skilled in the art would easily be able to use the described extract of the present invention with any of the solvent groups also described in the specification, taking the lead from the representative solvent of each of the groups described in the specification.

To meet the enablement requirement, the disclosing of any mode of making and using the invention is enough. Moreover, undue experimentation does not refer to the quantity of experimentation if it is routine work. In the present case, the working examples of the invention with representative of aqueous extract is described, and the working with the alcoholic and hydroalcoholic extract would be similar and considered routine work and cannot be regarded as "undue experimentation" in view of the teachings of governing case law. The description of

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working aqueous extract ought to be regarded as enabling for alcoholic and aqueous alcoholic extract in light of the governing case law. It is further respectfully submitted that the teachings from the case law points out that generic disclosure in the document is taken as enabling for similar moieties. The attention is specifically drawn to the holding enablement in *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 457 F.3d 1293, 79 US.P.Q.2d 1705 (Fed. Cir. 2006), where description of the adjuvants in the specification were found to be enabled even though specific examples with each of the adjuvant is not present. Accordingly, it is respectfully submitted that presence of demonstration of the aqueous extract and its working example fulfills the enablement requirement for alcoholic as well as aqueous alcoholic extracts.

In the specification preparation of the claimed composition is well described at page 25, line 25 through page 27, line 11. In particular, at page 26, line 21 through page 27, line 6, under the Table III, a typical nasal spray has been well described. In the Example-6 (page 29, lines 19-32 of the original specification), such a nasal spray is enabled through a working example.

The present formulation comprising the active ingredient has been shown to be efficacious during clinical trial in humans. A summary of clinical trial report is given below.

As per general practice followed in drug discovery, scientists carry out *in vitro* receptor binding studies and *in vivo* animal efficacy with the drug substance (test protocols do not favor evaluation of finished dosage forms in preclinical models).

Such a study is enabled in the specification as originally filed (*see in vitro* and *in vivo* descriptions at page 17, line 18 through page 27, line 11 of the originally filed specification), and any person skilled in the art would be able to follow the teachings of the specification without undue experimentation.

Even the receptor binding studies given in Table I, at page 19 of the specification was also carried out using the lyophilized extract [3].

Furthermore, the therapeutic potential of the final formulation consisting essentially of the said extract, in the form of a nasal spray as for an example, was exhibited in clinical studies following the teachings provided in the originally filed specification. The summary of the studies is provided by way of Declaration from Arora, the portions are reproduced below.

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The preparations of the alcoholic and hyrdoalcoholic extracts are enabled in the specification as originally filed. Examples 2, 3, and 4 of the specification as originally filed (*see* page 28, lines 6 through page 29, line 2) describe the extraction of pericarp of *Sapindus trifoliatus* in alcohols like n-butanol, iso-propanol, and aqueous ethanol, respectively. Following the teachings provided in the specification, extracts of *Sapindus trifoliatus* can be prepared by those of ordinary skill in the art without undue experimentation. For example, extracts of *Sapindus trifoliatus* were prepared in the laboratory in isopropyl alcohol (LL-7571), 50% ethanol (LL-7572) and n-butanol (LL-7573) following the teachings provided in the specification. The chemical composition and *in vitro* receptor binding profiles of these three extracts were compared with that of the aqueous extract. Chromatographic studies show that chemically the 50% aqueous-alcoholic extract is similar to the aqueous extract (*see* the Fig. 1 for TLC and Fig. 2 for HPLC below). The concentration of more polar compounds, however, are less in n-butanol and isopropyly alcohol (IPA) extracts. The binding profile of LL-7572 (i.e., 50% ethanolic extract) shows similarity to the profile exhibited by the aqueous extract of the present invention (*see* Table A of this Declaration for the receptor binding study at 250 μg/ml). This is consistent with the chromatographic profile mentioned above. Although LL-7571 and LL-7573 have receptor binding profiles not identical to the aqueous extract, the binding affinity was greater than 50% for at least four of the eight binding sites (Table A, receptor binding study).

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Fig. 1 : Thin layer chromatography of aqueous, alcoholic and hydroalcoholic extracts of the pericarp of *Sapindus trifoliatus*.

Spot no. (L to R)	Extract Taken	Sample ID
1	Aqueous Ext.	SKJ/28/33-1
2	IPA extract (LL-7571)	SKJ/28/33-2
3	50% Ethanolic Extract (LL-7572)	SKJ/28/33-3
4	n-BuOH Extract (LL-7573)	SKJ/28/33-4

TLC Condition

Concentration of sample : 15 mg/ml [MeOH : Water, 75:25]
TLC Plate : Silica gel 60 F254 [Merck]
Volume applied : 5µl
Solvent System (mobile phase) : Ethyl acetate: Methanol: Water: Glacial acetic acid

[8.5: 1: 0.5: 0.05]

Spray reagent : Vanillin Sulphuric acid

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Visualization : After heating at 110° C

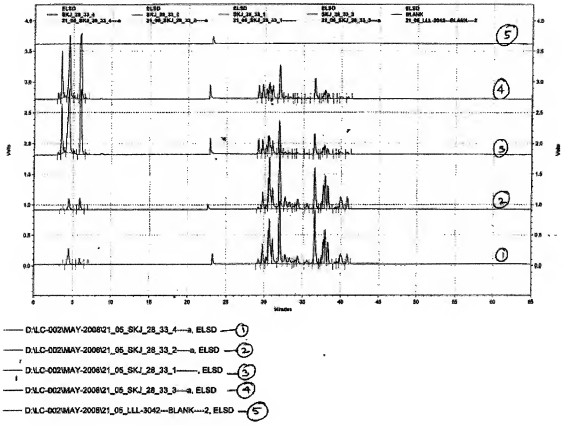

Fig. 2 : High performance liquid chromatography of aqueous, alcoholic and hydroalcoholic extracts of the pericarp of *Sapindus trifoliatus*.

Chromato-gram No.	Extract taken	Sample ID
1	n-Butanol extract (LL-7573)	SKJ-28-33-4
2	IPA extract (LL-7571)	SKJ-28-33-2
3	Aqueous extract	SKJ-28-33-1
4	50 % Ethanolic extract (LL-7572)	SKJ-28-33-3

HPLC conditions:

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Concentration of the sample	: 2.4 mg/ml in water
Column	: Purosphere STAR, RP-18, 5µ, 250 x 4.6 mm (MERCK)
Buffer	: 0.1 % formic acid
Mobile phase	: Buffer/Acetonitrile (Gradient system)
Flow	: 1ml/min
Injection volume	: 20 µl
Detector	: ELSD (Evaporation temp; 50°C ; Gain 8)

Table A: Receptor binding study at 250 µg/ml:

Receptor	% Inhibition			
	Aq. Extract of *S. trifoliatus* (*ref.* Table I, page 6)	**LL 7571**	**LL 7572**	**LL 7573**
GABA A, Agonist Site	102.40	95.74	99.35	96.04
Glutamate, AMPA Site	87.36	-9.45	46.60	-4.89
Glutamate, kainate Site	87.29	23.52	41.59	15.12
Glutamate, NMDA agonist Site	98.14	50.80	82.16	55.73
Glutamate, NMDA glycine (Strychnine insensitive) site	85.33	12.92	58.97	44.13
GABA chloride,TBOB	85.03	101.18	91.35	93.23
Glutamate chloride	89.49	44.48	23.28	21.29
Sodium site 2	69.54	96.07	76.20	96.35

** NOVASCREEN® (Caliper Life Sciences), USA, at which selected receptor binding affinity studies described in the specification (see page 18, lines 5-8), uses a criteria of 50% inhibition or greater to qualify a compound as active in binding experiments*

The Office Action recognizes that the specification describes an aqueous extract of *Sapindus trifoliatus* displays binding affinity for $GABA_A$ agonistic site in bovine cerebellum, and in Glutamate AMPA site in rat forebrain, Glutamate Kainate site in rat forebrain, Glutamate NMDA site in rat forebrain, Glutamate NMDA Glycine (strychenine-insensitive site) in rat cortex and hippocampus, GABA chloride TBOB in rat cortex, Glutamate chloride in rat cerebellum, and Sodium site 2 in rat forebrain when in higher concentrations (see page 19, Table 1). The Office Action states that there is no description of how these studies were conducted or how the results were obtained. As explained below, there are standard test protocols that a person of ordinary skill in the art would know about and would understand how to carry out in

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order to obtain and interpret results from the studies described in the specification as originally filed. Receptor binding studies of the extract of *Sapindus trifoliatus* demonstrated the ability to inhibit the binding of a selective radiolabeled ligand to the respective binding site and is measured as bound/unbound amount of radioactivity. For example, test substances are routinely evaluated for any binding towards GABA-A agonist site using its specific ligand, GABA, which is radioactively labeled with ^{3}H for the purpose of detection. This ligand binds to GABA-A agonist site with a particular affinity (in terms of the amount of radioactivity associated with the receptor preparation). In the presence of the *Sapindus trifoliatus* extract as demonstrated in the present invention, this binding may be either unaffected or reduced depending the relative affinities of the pharmaceutical preparation to the binding site in question. This study has been well described by Novascreen®, USA, under the *in vitro* studies at pages 17, line 18, through page 19, line 9, of the specification as originally filed, and the results are tabulated in Table I on page 19 of the originally filed specification. In that study, it was found that the extract of the present invention at a concentration 2.5μg/ml, reduced the binding of radioactively labeled GABA (^{3}H-GABA) to $GABA_A$ agonist site by 50.92%, which means that the said extract shares some affinity to $GABA_A$ receptor. At the same concentration (2.5μg/ml) the said extract did not significantly affect the binding of other radiolabeled ligands to their respective binding sites, indicating a greater affinity of the extract of the present invention to GABA-A receptor, as compared to other receptors. As previously noted, Novascreen®/Caliper Life Sciences, USA uses a criterion of 50% inhibition or greater to qualify a compound as active in binding experiments. A set of assay protocols for the respective receptors obtained from Caliper Life Sciences is attached as Exhibit 6. *See also* the website of Caliper Life Sciences (http://www.caliperls.com/products/contract-research/in-vitro/ion-channels/).

As explained below, the specification as originally filed enables one of ordinary skill in the art to practice the claimed invention and provide prophylactic treatment of migraine mediated through its anticonvulsant activity. Contrary to the Office Action contention that no working examples are shown with regard to the anticonvulsant pharmaceutical composition for nasal administration, examples are indeed provided that evaluated anticonvulsant activity in the

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maximal electroshock seizure model following intranasal administration of a lyophilized aqueous extract of *Sapindus trifoliatus*, in the pharmaceutically acceptable additive saline, to male Wistar rats – *see* page 20, line 7 through page 21, line 23 of the specification as originally filed. Similarly, the same solution was used to evaluate anticonvulsant activity in the pentylenetetrazole model – *see* page 22, lines 1-24 of the specification. Additionally, preparation for the claimed composition is well described from page 25, line 25, through page 27, line 11. In particular, on page 27 under Table III, a typical nasal spray has been elaborately described. In the Example 6, such a nasal spray is enabled through working example. The formulation comprising the active ingredient has been shown to be efficacious during clinical trial in humans, which is given below. Moreover, as per general practice in drug discovery by one skilled in the art, *in vitro* receptor binding studies and *in vivo* animal efficacy studies are carried out with the drug substance. Such a study is enabled in the specification (*see in vitro* and *in vivo* sections from page 17, line 18, through page 27, line 11, and a person of ordinary skill in the art would be able to follow the teachings of the specification without undue experimentation. Further, the receptor binding studies given in Table I, page 19 of the specification were carried out using the lyophilized extract [3]. Furthermore, in terms of determining which binding sites are responsible for the different aspects of seizure, as described on page 5, line 30, through page 6, line 19, herbal extracts act through multiple mechanisms. However, the therapeutic potential of the said extract in, for example, the form of a nasal spray, is exhibited in the clinical studies as described below.

Summary of Clinical Trials conducted with the composition/formulation of the present invention: A proof of concept study was conducted to evaluate the tolerability profile of 0.15%, 0.25%, 0.5%, 1% and 3% of nasal formulation of LLL-2011 (LLL-2011 is the extract [3] as disclosed in the specification as originally filed). The botanical drug product LLL-2011 was delivered as a nasal spray in Phase II clinical trials containing lyophilized aqueous extract of *S. trifoliatus*. Ten healthy subjects were randomized to each group. Drug concentrations of 0.15% to 1% were found to produce mild to moderate irritation of mucus membrane. Drug concentration of 3%, however, was found to produce severe irritation. Thus, the lowest dose and

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the highest dose in the tolerated dose range i.e., 0.15% and 1% nasal formulation of LLL-2011 were considered for further evaluation in phase I/II clinical trial to establish safety and efficacy. Since the formulations contain extract of *Sapindus trifoliatus* that is commonly used in various preparations, the Phase I study for tolerability profile and Phase II study for efficacy evaluation were reviewed together in migraine patients.

Primary objectives of the study:

To determine optimal dosage of LLL-2011 in reducing the frequency, intensity, duration and total pain index with two different doses of LLL-2011 as compared to placebo in the preventive treatment of common migraine.

Secondary objectives of the study:

To determine local as well as systemic tolerability of LLL-2011 at different dosage regimens of LLL-2011, and to determine frequency of requirement for rescue medication during the active treatment period.

Phase I/II clinical trial:

Data obtained from the studies conducted at reputed medical research centers in India, e.g., Post Graduate Institute of Medical Education and Research at Chandigarh, Sterling Hospital at Ahmedabad and Deenanath Mangeshkar Hospital at Pune are given below. The study design included placebo-control, randomized, double blind, and parallel group methodology. The study enrolled 151 patients of which 84 patients who completed the study were found to be suitable for statistical analysis. The patients were randomized to treatment groups consisting of 0.15% or 1% nasal formulation of LLL-2011 or placebo.

Results:

Results of the study demonstrate that LLL-2011 intranasal spray in the doses of 0.15% and 1% are effective in the prophylactic treatment of migraine. Significant reduction in migraine attacks from baseline was observed in LLL-2011 (0.15%) and LLL-2011 (1%) treatment groups.

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However, between groups statistical significance was not detected. Clinically, both LLL-2011 (0.15%) and LLL-2011 (1%) treatment groups showed more than 50% response rate in comparison to placebo response, which was <50%. The LLL-2011 (1%) formulation produced greater effect in reducing migraine attacks than the LLL-2011 (0.15%) formulation. Only 3 out of 42 patients on LLL-2011 (1%) treatment withdrew from the study due to local intolerance i.e., severe nasal burning sensation. Other adverse events reported were sneezing and itching. Otherwise both active formulations were moderately well tolerated.

The Declaration of Arora explains how the specification as originally filed enables one of ordinary skill in the art to practice the claimed invention and provide prophylactic treatment of migraines mediated through its anticonvulsant activity.

Predictability and State of the Art:

In Table I on page 19 of the specification as originally filed, eight binding sites were identified as of proposed antimigraine activity of *Sapindus trifoliatus*. Here, the binding data is functionally correlated with *in vivo* studies (MES model). In the specification, *Sapindus trifoliatus* is shown to have anticonvulsant activity in *in vivo* rat MES model (*see* page 20, lines 11-22). Based on published literature cited in the corresponding text, the same anticonvulsant activity is proposed to be due to binding of *Sapindus trifoliatus* towards Glutamate NMDA, Glutamate Kainate, Glutamate AMPA, Glutamate NMDA Glycine and Sodium site 2, as mentioned from lines 8-9 and 11-22 on page 20 of the specification as originally filed. However, the relevance and involvement of other binding sites, i.e., GABA A agonist site, GABA, Chloride, TBOB & Glutamate chloride, is available in various published literature as mentioned on page 5, line 23, through page 6, line 31. In addition, one of ordinary skill in the art would know how to perform human studies without undue experimentation as illustrated in the human studies were performed and reported in paragraph 11 above using the extract [3] as disclosed in the specification as originally filed following the teachings of the present application. It is respectfully submitted that it is not necessary to extrapolate the effects of *Sapindus trifoliatus* extracts on the prophylactic treatment of migraine only from animal studies.

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Epilepsy and migraines "share several clinical features and in many instances, respond to the same pharmacological agent." (*See* page 5, lines 17-18 of the specification as originally filed). Thus, drugs known for the treatment or prevention of epilepsy, such as anticonvulsants, would also have a reasonable expectation of success for treatment or prevention of migraines. For example, as explained on page 5, line 30 through page 6, line 19 of the specification, anticonvulsant drugs such as sodium valproate and gabapentine have been demonstrated to be effective at preventing migraines by modulating GABA neurotransmission, and topiramate has been under investigation as a prophylactic agent for migraines as a result of its interaction with AMPA/Kainate glutamate receptors and GABA-A receptors. The extract of *Sapindus trifoliatus* was shown in Table 1 to have effective binding affinities for "receptor sites viz. GABA-A agonist site, Glutamate-AMPA site, Glutamate-Kainate site, Glutamate-NMDA agonistic site, Glutamate-NMDA glycine (strychnine insensitive) site and Sodium channel (site 2), which are known to have major mediatory role in anticonvulsant activity." (Page 9, line 28 through page 10, line 2). One of ordinary skill in the art would have a reasonable expectation that the *Sapindus trifoliatus* extract could act as a prophylactic agent for migraines because migraines and epilepsy often respond to the same drugs and the *Sapindus trifoliatus* extract has high binding affinities for receptor sites that mediate anticonvulsant activity.

The Declaration of Arora explains why the animal studies conducted and described in the specification, as originally filed, provides reasonable prediction of success of the effect of the claimed anti-migraine medication in humans. The Declaration of Arora explains why the claim-designated compositions may be useful for providing such an effect.

Amount of Experimentation Necessary: The quantity of experimentation necessary to carry out the claimed invention is low, and the skilled artisan could rely on the instant specification in combination with prior art on how to make and use the claimed pharmaceutical composition for nasal administration. *See* Declaration of Arora.

As to the guidance of the specification and existence of working examples, the Examiner has mentioned that there is no description as to how the studies on the binding affinity were conducted or how the results were obtained. It is respectively submitted that at page 18 of the

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originally filed specification it is mentioned that *in vitro* receptor binding studies reveal the binding affinity of the extract (3), which has mediatory role in anticonvulsant activity. As mentioned above the said affinity studies were carried out at Novascreen and the basis of their study and correlation with binding affinity were provided in the prior response dated September 25, 2007. Applicants submit once again that those of ordinary skill in the art, following the teachings of the originally filed specification, would know how to conduct such studies and correlate the specific binding affinities without undue experimentation. The results thus obtained are provided in Table I of the originally filed specification at page 19. Accordingly, it cannot be said that how the studies were conducted and results obtained were not known to those of ordinary skill in the art.

Preparation of the aqueous, alcoholic and hydroalcoholic extracts of *Sapindus trifoliatus* are described in detail on page 15, line 26, through page 16, line 8, of the specification as originally filed. The preparations of such extracts are exemplified in the Examples 1 through 4, and the preparation of a nasal formulation is enabled in Example-6 from lyophilized aqueous extract [3]. Further, the preparation of identical formulations by substituting the extract [3] with any of alcoholic or hydroalcoholic extracts is within the ability of one of ordinary skill in the art. The preparation of batches of nasal spray containing a *Sapindus trifoliatus* extract is described in detail on page 25, line 21 through page 27, line 6. The administration of the pharmaceutical formulation is disclosed on page 27, lines 9-11. In view of the specificity of the claimed invention and detailed guidance provided by the specification as well as the level and knowledge of one of ordinary skill in the art, the skilled artisan would not have to conduct an undue amount of experimentation to make and/or use the claimed invention.

In view of the specificity of the claimed invention and detailed guidance provided by the specification as well as the level and knowledge of one of ordinary skill in the art, the skilled artisan would not have to conduct an undue amount of experimentation to make and/or use the claimed invention. The rejection under 35 USC 112, first paragraph, for lack of enablement should be withdrawn.

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Claims 1-6, 10, 11 and 21-25 were rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Claim 1 has been amended to now claim "a pericap of the fruit," thereby removing the lack of antecedent basis for the feature "the pericap of the fruit" in claim 1 and thereby rendering this rejection moot.

Claim Rejection – 35 USC 103(a)

It is respectfully submitted that the Declaration of Arora does demonstrate non-obviousness of the claimed invention over Chikara. The Office Action does not properly recognize the evidence that Chikara teaches away from the claimed invention. There would have been no reason for one of ordinary skill in the art to deviate from the teaching of Chikara. Thus, there would have been no reasonable expectation of success in deviating from the teaching of Chikara. *See* Declaration of Arora.

Since Applicants have fully enabled the invention they are claiming, the teachings of Chikara are not the only teachings that provide enablement for Applicants' invention. Therefore, the Chikara rejection does not teach or suggest the invention for which Applicants have enabled.

Contrary to the Office Action, Applicants have shown that an aqueous extract of *Sapindus trifoliatus* provides the instantly claimed effects, and therefore Applicants have fully enabled the invention they are claiming. *See* Declaration of Arora.

The claims of the present application are styled in "consisting essentially of" form. As indicated in MPEP section 2111.03, this term is intended to limit the scope of the claims to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. *See In re Herz*, 537 F.2d 549, 551-552, 1990 U.S.P.Q. 461, 463 (C.C.P.A. 1976). In the present case, it is undisputed that the Chikara [previously referred to as Gupta] reference discloses a composition that includes *Sapindus trifoliatus* and *Emblica officinalis*. As demonstrated by the data submitted herewith in the Declaration of Sudershan K. Arora, the presence of the *Emblica officinalis* in the composition disclosed by Chikara is indeed sufficient to destroy the basic novel characteristics of the claimed invention.

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Specifically, the presence of *Emblica officinalis* significantly affects receptor binding properties of a composition that includes *Sapindus trifoliatus*. Chikara therefore not only fails to disclose the present invention, Chikara teaches directly away from the present invention.

As specified by claim 1, the claimed composition possesses affinity for at least one receptor selected from the group consisting of Gamma-Amino Butyric Acid (GABA)-A agonist site, Glutamate-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) site, Glutamate-Kainate site, Glutamate-*N*-methyl-D-aspartic acid (NMDA) agonistic site, Glutamate-*N*-methyl-D-aspartic acid (NMDA) glycine (strychnine insensitive) site and Sodium channel (site 2). As set forth in Exhibit 1 to the enclosed Declaration of Dr. Arora, a criterion of 50% inhibition or greater is used to qualify a compound as being active in binding experiments.

Table 1 of the present application is excerpted below:

Table 1:

S.No.	Receptor	Percent inhibition with *Sapindus trifoliatus*	
		2.5 µg/ml	250 µg/ml
1	GABA A, agonist Site	50.92	102.40
2	Glutamate AMPA Site	5.43	87.36
3	Glutamate Kainate Site	-15.70	87.29
4	Glutamate NMDA agonist Site	7.27	98.14
5	Glutamate NMDA glycine (Strychnine insensitive) site	14.50	85.33
6	GABA chloride TBOB	-5.12	85.03
7	Glutamate chloride	-2.72	89.49
8	Sodium site-2	19.98	69.54

Note that inhibition is above 50% for all of the indicated receptor sites at 250 µg/ml.

In contrast, receptor binding affinity with the anti-migraine formula mentioned in the Chikara patent is reported in the Arora Declaration. Table 3 from that Declaration is reproduced hereinbelow:

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Table 3: Receptor Binding affinity with the antimigraine formulation mentioned in Chikara et al patent.

S.No.	Receptor	Percent inhibition (Chikara et al composition)	
		2.5 µg/ml	250 µg/ml
1	GABA A, Agonist Site	19.21	**95.95**
2	Glutamate, AMPA Site	-0.89	41.69
3	Glutamate, kainate Site	-1.16	25.68
4	Glutamate, NMDA agonist Site	15.26	**66.02**
5	Glutamate, NMDA glycine (Strychnine insensitive) site	4.03	42.60
6	GABA chloride,TBOB	-14.60	-3.77
7	Glutamate chloride	1.95	**84.35**
8	Sodium site 2	13.37	3.30

The differences in the foregoing data are striking. At 250 µg/ml, the composition of the invention exhibited greater than 50% inhibition for all of the referenced binding sites. In sharp contrast, the Chikara composition met this criterion only for three of the eight sites, and of those, binding affinity was reduced relative to the inventive composition.

From the above data, it is beyond dispute that the presence of *Emblica officinalis* does indeed affect the basic and novel characteristics of a composition made with *Sapindus trifoliatus* extract. It is noted further that the data in the Arora Declaration demonstrates that hederagenin in the Chikara composition originates from the *Sapindus trifoliatus*, and its presence is not due to *Emblica officinalis*. Chikara thus further teaches away from the presently claimed invention.

The Arora Declaration also contains toxicology data and a second HPLC analysis. The second HPLC analysis demonstrates that the amount of hederagenin in one of the formulations of the invention is significantly and unexpectedly higher than that of the cited art. The toxicology data demonstrates that the tested compound of the invention did not exhibit nasal irritation, and hence is useful for nasal application.

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The Examiner states in the Office Action that "using a desired form of an extract" and "adjusting the pH of a solution" are "deemed merely a matter of judicious selection and routine optimization." Applicants respectfully disagree with the Examiner's comments, and submit that the Examiner's analysis is off the mark. The claims of the present application, styled in "consisting essentially of" form, have been drawn to exclude the *Emblica officinalis* extract that is specifically mandated by the Chikara reference. Based on the data of record, all claims of the present application are allowable.

Applicants note that hederagenin in fact is an indirect estimation of the total triterpenoid saponins present in the *Sapindus trifoliatus* extract. Saponins are glycosides of steroids, steroidal alkaloids or triterpenes found in plants. In cases of triterpenoid saponins the glycoside units are linked to the triterpene moiety (known as aglycone) at its C-3 position (*see* Exhibit 7, Trease and Evans' Pharmacognosy, Fourteenth edn., Page 293).

However, on hydrolysis of saponins, free aglycone is obtained. By measuring the concentration of the aglycone moiety one can arrive at a particular concentration of the total saponins present in an extract.

In a few occasions the aglycone part of the saponin is hederagenin. Therefore, the applicants would like to emphasize here that hederagenin is a natural product known in the art and the present invention is not directed to the same *per se*. To reiterate, in accordance with the present invention, fruit pericarp of the plant *Sapindus trifoliatus* is extracted in water or alcohol or in a mixture of water and alcohol. What is obtained is a specific range of concentration of a mixture of triterpenoid saponins in the extract. The aglycone part in all saponins is hederagenin (*see* compounds 5-10, page 16 –17 of the specification as originally filed).

The extract obtained in the present invention possesses anticonvulsant activity. It is important for any therapeutic activity to deliver a known quantity of the active substance. In this case, by knowing the quantity of sugars and aglycon, since the ratio is the same, the concentration can be measured through the hederagenin obtained by the acid hydrolysis of the saponins. Hence, the saponin quantity in the extract is measured by estimating the hederagenin content (see lines 20-30 of page 16 and lines 1-13 of page 17 of the specification as originally

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filed). This is further evident from Row No. 2 of Table III at page 27 of the specification, wherein the active ingredient saponin strength is expressed in terms of % w/v hederagenin content. Thus, measurement of hederagenin is an indirect estimation of the triterpenoid saponins present in the extract. It has been observed that the extract obtained by following the process of the present invention typically contains a mixture of triterpenoid saponins that, when expressed in terms of hederagenin, is in the range of 4-8% w/w of hederagenin. The pharmaceutical composition of the present invention derived from the same extract typically contains such saponins that, when expressed in terms of hederagenin in a similar manner, is in the range of "0.001-1% w/v of hederagenin." In view of the foregoing, claim 1 has been amended to claim **"an aqueous, alcoholic, or hydroalcoholic extract of the pericarp of the fruit of Sapindus trifoliatus, comprising of total saponins estimated as hederagenin ranging from 0.001 to 1.0 (%w/v), and....."**

The Declaration of Arora mentions that total saponin content was analyzed as hederagenin (see page [insert] of the Declaration of Arora under "Preparation of the sample"). This is consistent to the disclosure of the specification as originally filed at page 17, lines 6-13.

The Examiner contends that hederagenin would be inherently present in *Sapindus trifoliatus* and hence there is no invention in using the same. The Examiner contends that the applicants have not shown that aqueous extract of *Sapindus trifoliatus* provides the instantly claimed effects and therefore has not enabled their invention they are claiming and hence it is only the cited art which is enabling. As noted above, the aqueous extract of *Sapindus trifoliatus* provides enabling disclosure as to the binding affinity as well as providing the anticonvulsant activity. Accordingly, the submissions and the Declaration of Arora should to be accepted. That anticonvulsant activity is related to prophylactic treatment of migraine is already provided in the Background of the Invention as originally filed, applicants respectfully draw the Examiner's attention to the same to correlate the working examples of the invention. In other words, the present invention shows anticonvulsive activity of the composition and demonstrates anti-convulsive activity to be related to prophylactic treatment of migraine. Accordingly, the inventors claim the composition for prophylactic treatment of migraine.

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Applicants continue to traverse the restriction requirement. It is submitted that the restriction requirement should be withdrawn, especially in light of the foregoing. Unity of invention is found in the subject application.

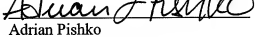
Conclusion

All rejections having been addressed, applicants respectfully submit that this application is in condition for allowance.

Respectfully submitted,

BANNER & WITCOFF, LTD.

Dated: June 11, 2008

By: 

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